REMARKS

In this Amendment, claims 22, 38, 40, 41, 43-45 have been amended, claim 39 was previously presented and claims 1-21, 23-37, 42 and 46-63 have been canceled without prejudice or disclaimer. In addition, claims 64-92 are newly presented. Accordingly, the currently pending claims are now claims 22, 38-41, 43-45 and 64-92. It is submitted that no new matter has been introduced into the application by virtue of the amended and new claims, which are supported by the prior claims and the originally filed disclosure. Applicants further reserve the right to timely file divisional application(s) covering the non-elected subject matter in the instant application.

Support for the amended and new claims

Claim 22 has been amended to reflect the correct dependency in view of the newly presented claims. Support for amended claim 38 is found in the instant specification, *inter alia,* on page 18, [0051]. Support for amended claim 41 is found in the instant specification, *inter alia,* on page 9, [0027]. Claims 43-45 have been amended to contain proper dependency and claim language. New claims 64 and 70 find basis in the instant specification and in prior claim 10. New claim 65 finds basis in the specification and in prior claims 21 and 53.. New claims 66 and 67 find basis in the specification and in prior claim 49. New claim 68 finds basis in the specification and in prior claim 48. New claim 69 finds basis in the specification and in the specification and in prior claim 50. New claim 71 finds basis in the specification and in prior claim 54. New claim 72 finds basis in the specification and in prior claim 55. New claim 73 finds basis in the specification and in prior claim 56. New claim 74 finds basis in the specification and in prior claim 57. New claim 75 finds basis in the specification and in prior claim 58. New claim 76 finds basis in the specification and in prior claim 59. New claim 77 finds basis in the specification and in prior claim 60. New claim 78 finds basis in the specification and in prior claim 61. New claim 79 finds basis in the specification and in prior claim 61. New claim 80 finds basis in the specification and in prior claim 62. New claim 81 finds basis in the specification and in prior claim 63. New claims 82 and 83 find basis in the specification and in the instant specification, *inter alia,* on page 18, [0051]. New claim 84 finds basis in the instant specification, *inter alia,* on page 4, [0011] and pages 8-9, [0026].

New claim 85 finds basis in the instant specification, *inter alia,* on page 4, [0013]. New claims 86-92 find basis throughout the instant specification, including Examples 1-10, and in prior claims 21, 38, 40 and 46.

In the Remarks below, the May 3, 2004 Office Action has been considered as if it pertains to newly presented claims 64-92. Thus, this Amendment is responsive to the May 3, 2004 Office Action as if it applies to the new claims.

Objection to the Disclosure

The abstract of the disclosure was objected to because of the use of "describes" or "described". Applicants have amended the abstract to avoid the use of these terms. Accordingly, the objection to the disclosure has been overcome.

Objection to Claim 45

Claim 45 was objected to because of the recitation of "further". Applicants have amended this claim to remove the language that was objected to. Accordingly, the objection to claim 45 has been overcome.

The claims fulfill the requirements of 35 U.S.C. §112, first paragraph

Claims 21, 22 and 38-63 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The Examiner opines that based on upon the limited disclosure, the level of skill, and the breadth of the claims, undue experimentation would be required to practice the invention.

Applicants respectfully disagree and point out that the presently claimed invention is directed to preparations and compositions comprising muscle-derived stem cells and a physiologically acceptable matrix material admixed at the point of service to form a muscle-derived stem cell biomatrix. Applicants' biomatrix can be implanted and innervated and creates new 2- and 3-dimensional structures that are formed without having to incubate or culture the muscle-derived stem cells and the matrix material for more than about 12 hours prior to use. The biomatrix can be used for the treatment or repair of a number of types of

tissues and organs. It is submitted that the claims as presented herein are enabled by Applicants' disclosure.

Several factual inquiries have long been considered in the determination of whether making and using an invention would have required undue experimentation, and thus whether a disclosure is enabling under 35 U.S.C. § 112, ¶ 1. *In re Cortright,* 165 F.3d 1353, 1356 (Fed. Cir. 1999). Such factual inquiries include (1) the quantity of experimentation necessary; (2) the amount of direction or guidance provided; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). It is to be noted that the above factors are considered to be illustrative, not mandatory, and that not all of the factors require review. *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

In the instant case, Applicants submit that the present claims are not overly broad in view of the teaching and guidance provided in the specification and the numerous working examples that are described. Applicants also submit that the level of skill in this art is quite high. For example, those practicing the present invention are likely to be M.D.s and/or Ph.D.s who are able to obtain the muscle-derived cells and admix them with a suitable physiologically acceptable matrix material to form the novel muscle-derived stem cell-biomatrices as described and claimed by the Applicants. The practitioners in the pertinent art of tissue and organ treatment or repair are also highly skilled and would be likely to possess an M.D. and/or a Ph.D. degree. In addition, the state of the art is at a level at which those having skill in the art know and understand how to isolate and obtain cells from various tissues and organs and how to utilize or administer the cells in a variety of clinical and medical treatments, in both human and non-human mammals. Those skilled in this art also are familiar with the use of glue materials, e.g., fibrin glue, Dermabond®, BioGlue®, for wound and surgical treatments, for example. Armed with this knowledge and teaching, those having skill in the pertinent art would be able to readily understand and practice Applicants' claimed invention without undue or excessive experimentation.

Given that the level of skill in the art is high and that Applicants provide clear guidance for the practice of the presently claimed invention through the teachings and exemplification in the instant specification, an undue amount of experimentation is not required to practice the invention as presently claimed. Moreover, there is a reasonable expectation of success in view of the description in the disclosure and the several working examples described by the Applicants.

Specifically, Applicants teach several muscle-derived stem cell biomatrix compositions and preparations whose properties and functions were demonstrated *in vitro* and *in vivo*, as described in the instant specification. Illustratively, Applicants exemplify a muscle-derived stem cell and alginate matrix composition and preparation (Example 1, page 19; Example 6, page 22); a muscle-derived stem cell and SIS matrix composition and preparation (Example 2, page 20; Example 4, page 21; and Examples 7-10, pages 22-29); and a muscle-derived stem cell and fibrin glue matrix composition and preparation (Example 3, pages 20-21). These muscle-derived stem cell biomatrix compositions and preparations were demonstrated to provide viable stem cells that survived over time in the matrix compositions and preparations (e.g., Examples 1 and 7-10). The functionality of the muscle-derived stem cell biomatrix compositions and preparations is exemplified by their ability to induce wound healing and tissue repair (Example 1), to remodel a SIS matrix so as to improve its biomechanical properties (Example 8, pages 23-26), to generate a calcium-dependent contractile activity (Example 9, pages 26-27 and Fig. 2) and to ameliorate stress urinary incontinence *in vivo* by restoring muscular function and innervation to damaged sphincter muscle in an art-accepted animal model. (Example 10, pages 28-29).

It has long been established that every embodiment or aspect of an invention need not be exemplified in a disclosure. Also, a large number of examples is not required in order to satisfy the enablement requirement. *In re Robins*, 429 F.2d 452, 166 USPQ 552 (CCPA 1970). In view of the high level of skill in the relevant art, the knowledge in the art at the time of the invention, the teaching and exemplification in the instant disclosure for preparing the claimed muscle-derived stem cell and matrix material compositions and preparations (e.g., Examples 1-10), and the use and function of these compositions and preparations both *in vitro* and *in vivo*

(Examples 1-10), it is submitted that the specification enables the presently claimed invention to be practiced in a manner commensurate with the scope of the claims, and that no undue experimentation is required to practice the invention as presently claimed.

Additionally, Applicants submit that the results described in the examples show that the claimed compositions and preparations allowed wound healing to occur (Examples 1 and 6), allowed the continued growth of the muscle-derived stem cells to form myotubes on an exemplified matrix material (Examples 2 and 7) and allowed restoration of muscular function and innervation to a damaged sphincter in an art-recognized animal model (Example 10). In view of the foregoing, Applicants respectfully disagree with the Examiner's remarks on page 6, first paragraph, of the Office Action and respectfully point out that a mechanism of action is not required for an enabling disclosure that supports the full scope of the claimed invention.

Further, Applicants teach ways in which allogeneic cells may be tolerated by a recipient. (See, e.g., page 9, [0027], of the instant disclosure). Thus, combined with the knowledge of those having skill in the relevant art, Applicants provide sufficient guidance and teachings within the instant specification to embrace the use of allogeneic cells in the compositions and preparations of the presently claimed invention. In view of this knowledge and teaching, the presently claimed invention is supported by the specification and no undue experimentation is required to practice the invention as presently claimed.

Based on Applicants' specification, exemplification, and explanation, it is submitted that Applicants have indeed provided reasonable detailed description and a number of working examples to enable those having skill in the art to practice the presently claimed invention without excessive or undue experimentation. In view of the foregoing, Applicants respectfully submit that one having skill in the pertinent art could employ their skill, without resorting to undue or excessive experimentation, to practice the invention as described and claimed by Applicants.

Applicants therefore respectfully submit that all of the present claims satisfy the requirements of 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the §112, first paragraph rejection are respectfully requested.

The claims fulfill the requirements of 35 U.S.C. §112, second paragraph

Claim 38 was rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. According to the Examiner, the term "innervatable" is vague and indefinite and cannot be found in a standard English dictionary.

Applicants respectfully disagree with this rejection. The term "innervatable" has as its root the verb "innervate" having the definition: "to supply with nerves", according to a standard dictionary, i.e., Merriam Webster's Collegiate Dictionary, Tenth Edition, 2002, Merriam Webster, Inc. Also, according to this dictionary, the suffix "able" is defined generally as "capable of, fit for, or worthy of (being so acted upon or toward) – chiefly in adjectives, derived from verbs…".

Thus, the term "innervatable", as would be understood by the skilled practitioner based on its common meaning, is understood to mean "capable of being innervated", i.e., capable of being supplied with nerves. It is respectfully submitted that the term innervatable requires no special definition and would be readily understood by the skilled person in the art, who would be able to ascertain the metes and bounds of a claim containing this term. Accordingly, withdrawal of the rejection is respectfully requested.

The claims fulfill the requirements of 35 U.S.C. § 102

Claims 21, 22, 38, 40-44, 46-56 and 61 were provisionally rejected under 35 U.S.C. §102(e) as allegedly being anticipated by copending application U.S. Serial No. 09/549,937 (hereinafter "the '937 application").

It is well established that to anticipate under §102, each and every limitation of a claimed invention must be disclosed in a single reference. *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 57 USPQ2d 1057 (Fed. Cir. 2000; *Brown v. 3M*, 265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001).

Applicants submit that the presently amended and newly presented claims are patentably distinct from the disclosure of the '937 application. The cited passages of the '937

application and claim 115, as referred to by the Examiner, do not remotely teach or suggest the presently claimed preparations comprising muscle-derived stem cells and a physiologically acceptable substrate material forming an implantable and innervatable biomatrix comprising a two- or three-dimensional scaffolding for tissue and organ treatment or repair. Additionally, the '937 application does not teach or suggest the presently claimed compositions comprising muscle-derived stem cells and a physiologically acceptable matrix material, in which the muscle-derived stem cells are incubated with the physiologically acceptable matrix material *in vitro* for less than about 12 hours prior to use to form a muscle-derived stem cell biomatrix, as described in the instant application.

It is submitted that it is the Applicants who unexpectedly discovered and teach that following admixture and without a long-term incubation, (i.e., greater than about 12 hours), the muscle-derived stem cell biomatrix permits the formation of new structures such that the biomechanical properties of the preparation or composition are changed to create new 2- and 3-dimensional tissue and organ structures. (See, e.g., the instant specification on page 18, [0051]. There is also no recognition or teaching in the '937 application that a muscle-derived stem cell biomatrix as newly described by Applicants exhibited contractility and innervation, so as to provide new materials having new and useful properties for the treatment or repair of damaged tissues and organs, and the healing of wounds.

Because the '937 application fails to disclose each and every element of applicant's claimed invention, arranged as in the claim, this reference does not anticipate the present claims. Accordingly, reconsideration and withdrawal of the §102(e) rejection are respectfully requested.

Claims 21, 22, 38, 40-44, 46-56 and 61 were also rejected under 35 U.S.C. §102(f) as allegedly not being invented by the Applicant. The Examiner alleges that the cited patent application (USSN 09/549,937) and the instant claims are drawn to the same subject matter, but that the cited application has a different inventive entity.

Applicants respectfully disagree that the '937 application and the instant claims are drawn to the same subject matter. The distinctions between the presently claimed invention and the teaching of the '937 application have been addressed hereinabove.

To reiterate, Applicants were the first to describe their novel invention directed to preparations comprising muscle derived stem cells and a physiologically acceptable substrate material forming an implantable and innervatable biomatrix comprising a two- or three-dimensional scaffolding for tissue and organ treatment or repair, and to compositions comprising muscle-derived stem cells and a physiologically acceptable matrix material, in which the muscle-derived stem cells are incubated with the physiologically acceptable matrix material *in vitro* for less than about 12 hours prior to use, thus forming a muscle-derived stem cell matrix. The presently claimed invention is distinct from the teachings of the '937 application and furthers knowledge, understanding and utility in the art by providing muscle-derived stem cell biomatrix preparations and compositions that (i) advance the field of tissue engineering, (ii) can be rapidly produced, and (iii) can be employed at the point of service in treating or repairing damage to tissues and organs. (See, e.g., page 4, [0012], page 6, [0020], page 7, [0021]).

Because the '937 application fails to disclose each and every element of Applicant's presently claimed invention, arranged as in the claim, the '937 application and the instant claims are not drawn to the same subject matter. Applicants presently claimed invention provides novel compositions and preparations, which are not anticipated by the '937 application under 35 U.S.C. §102(f). Accordingly, withdrawal of this rejection is respectfully requested.

The claims fulfill the requirements of 35 U.S.C. § 103

Claims 21, 22 and 38-63 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ye et al. (2000, *European J. Cardio-thoracic Surgery*, 17:449-454; hereinafter "Ye et al."), or Atala (U.S. Patent No. 6,482,645, hereinafter "the '645 patent"), or Vandenburgh (U.S. Patent No. 6,503,504, hereinafter "the '504 patent"), in view of McDowell et al. (U.S. Patent No. 6,171,340, hereinafter "the '340 patent"), and WO 99/56785, and as

evidenced by Capelli et al. (U.S. Patent No. 5,045, 601, hereinafter "the '601 patent") and Humes et al. (US/2002/0090389, hereinafter "the '389 application"). The Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify the methods taught in the above references "by simply using muscle stem cells as the type of stem cells and SIS as the type of substrate to make a tissue repair composition with a reasonable expectation of success."

Applicants respectfully disagree and point out that this rejection of obviousness in view of the above-cited references appears antithetical to the Examiner's rejection of the specification as not enabling the Applicants' claimed invention. Notwithstanding, Applicants submit that the cited references alone or in combination do not make obvious Applicants' invention as presently claimed.

The presently claimed invention is directed to new and useful preparations and compositions not before recognized or contemplated by the art. Applicants' novel preparations comprise muscle-derived stem cells and a physiologically acceptable substrate material forming an implantable and innervatable biomatrix comprising a two- or three-dimensional scaffolding for tissue and organ treatment or repair. Moreover, Applicants' novel compositions comprise muscle-derived stem cells and a physiologically acceptable matrix material in which the muscle-derived stem cells are incubated with the physiologically acceptable matrix material *in vitro* for less than about 12 hours prior to use, to form a muscle-derived stem cell matrix.

Applicants' inventive muscle-derived stem cell biomatrix, in a short time period (i.e., less than about 12 hours) after combination of the component muscle-derived stem cells and physiologically acceptable matrix or substrate material, unexpectedly allows the formation of new structures in which the biomechanical properties of the matrix or scaffold are changed and new 2- and 3-dimensional tissue and organ structures are created. (See, e.g., page 18, [0051] of the instant specification). Further, the rapid formation of a useful biomatrix preparation or composition reflects a surprising synergy between the muscle-derived stem cells and the matrix or substrate material, which alleviates the requirement for long duration incubation and/or

extended culturing periods prior to using Applicants' claimed biomatrix compositions and preparations.

It is pointed out that prior to Applicants' discovery of the presently claimed invention, the preparation of cell matrix materials required long time periods to engineer tissues or matrices for implantation and to monitor the growth and maintenance of the cells. (See, e.g., the instant specification on pages 2-3, [0005]-[0009]. Importantly, the presently claimed invention overcomes problems in the art which involve routine delays in the preparation of cell matrix compositions involving other cell types. As explained by Applicants, such delays and problems result from the need for cells to grow, maintain homeostasis, attain confluence, and/or to seed a substrate prior to use. (*Id.*, at pages 2-3).

The cited art, alone or in combination, does nothing to negate the patentability of the presently claimed invention in view of this art. More specifically, Ye et al. teaches the formation of cell sheets by culturing cells from human aortic tissue over a 4-week time period. Thereafter, these cell sheets are folded into four layer sheets, mounted on culture frames and cultured for another four weeks, as described by Ye et al. on page 450, column 1, Section 2.2, and as shown in Fig. 1 of Ye et al. Thus, Ye et al., which requires long time periods to form the described cell sheets into tissue-like structures, suffers from the very problems and delays in the art that are described and overcome by the Applicants' invention.

Also and importantly, Ye et al. teaches away from the presently claimed invention, since the object of the work of Ye et al. is to assemble cells into tissue-like structures, which serve as a template for further tissue development without any scaffold materials. Specifically, as stated by Ye et al.:

"The aim of this study is to develop a new method for a three-dimensional completely autologous human tissue without using any scaffold materials." (page 450, column 1, lines 6-8).

Applicants therefore submit that the teaching of Ye et al. is clearly distinct from, and contrary to, the presently claimed invention. Thus, Ye et al., taken alone or in combination with the other cited references, does not negate the patentability of Applicants' presently claimed invention.

The '645 patent to Atala describes the use of two cultured cell populations to produce artificial fascial slings. The slings contain both collagen-secreting cells on a substrate and elastin-secreting cells layered thereon so as to form a chimeric interface. (Col. 2, lines 3-20). Moreover, the slings as described in the '645 patent require polylayers or arrangements comprising multiple layers of homogeneous cultured cell populations that are superimposed over each other. (Col. 3, lines 41-65). The preparation of the artificial fascial slings requires repeated culturing techniques over lengthy time periods, e.g., "12 hour *intervals*", as described at Cols. 9-10, Example 3 of the '645 patent. The slings contemplated and described in the '645 patent are not remotely similar to the inventive muscle-derived stem cell biomatrix preparations and compositions that are described and claimed by the Applicants. Thus, the '645 patent, taken alone or in combination with the other cited references, does not negate the patentability of Applicants' presently claimed invention.

The '504 patent to Vandenburgh describes organized tissues ("organoids) and methods of preparing such tissues in which extracellular matrix components are mixed with cells, some of which contain a foreign DNA sequence. The resulting cell suspension is placed in a vessel whose 3-dimensional geometry approximates the gross morphology of the tissue, and which also contains tissue attachment surfaces thereon. (Col. 1, lines 63 to Col 2, lines 1-5; Col. 3, lines 45-57). The organized tissue contemplated and described in the '504 patent involves substantially post-mitotic cells, in which at least 50% of the cells containing a foreign DNA are non-proliferative. (Col. 5, lines 54-67). Thus, the '504 patent teaches away from stem cells and further requires a discrete apparatus or vessel (e.g., Col. 9 and Fig. 1 of the '504 patent) for organoid formation. The formation of the non-proliferating cell-containing organoids involves processes that require long preparation, culturing and incubation times (Cols. 8-12 of the '504 patent).

The organized tissues taught and disclosed in the '504 patent are completely distinct from Applicants' claimed invention, which satisfies a need for point of service preparations and compositions as described and claimed by Applicants. Specifically for example, Col. 11, lines 25-30 of the '504 patent teaches that before the organoids were ready for implantation, some were cultured in maintenance media containing cytosine arabinoside for the "final four to

eight days", to eliminate proliferating cells. This teaching and disclosure are completely disparate and distinct from the muscle-derived stem cell biomatrix compositions and preparations of the presently claimed invention. In view of the clear and profound differences between the teachings of the '504 patent and Applicants' claimed invention, the '504 patent does not remotely negate the patentability of the present invention, either alone or in combination with the other cited references.

The secondary references of McDowell (the '340 patent) and WO 99/56785 do not make up for the many deficiencies in the above-described primary references. Combining the disparate teachings of the '340 patent with those of WO 99/56785 and the above-described references would not motivate or compel the skilled person in the art to make the modifications that would be necessary to arrive at Applicants' novel invention with a reasonable expectation of success. The '340 patent teaches articulating joint repair in which cartilage can be repaired and cells can be delivered to the site of repair by attaching them to prosthetic shields and/or spacers as described in the patent. (Col. 2, lines 53-67; Col. 3, lines 10-30; Col. 7, lines 14-30). The shields and spacers as contemplated in the '340 patent are shown in the patent's figures. When considered in its entirety, the teaching of the '340 patent, alone or in combination with the other cited references, does not compensate for the complete lack of teaching and suggestion of the other references, and does not make obvious Applicants' invention as claimed.

WO 99/56785 teaches muscle-derived cells that can be genetically engineered to deliver biomolecules to tissues, as well as their method of preparation and use in muscle tissue repair. WO 99/56785 is silent regarding Applicants' presently claimed invention which provides point of service compositions and preparations that were newly found to have unexpected properties and advantages upon admixture and use for tissue and organ treatment or repair. More specifically, Applicants have unexpectedly discovered that functional muscle-derived stem cell and matrix material compositions and preparations form stable biomatrices having altered biomechanical properties so as to provide 2- and 3-dimensional structures that exhibit contractility and can be innervated, thus enhancing their function.

Finally, the '601 patent to Capelli et al. teaches a polymer adhesive composition with properties of moisture vapor permeability and stability in water, and methods of its production. The '389 application to Humes et al. teaches an implantable, intravascular device, comprising an anchor for immobilization on a blood vessel wall and a cartridge containing an agent that can modify a pre-selected molecule (e.g., remove a pre-selected molecule from the bloodstream). Neither the '601 patent nor the '389 application, alone or in combination, teaches or suggests Applicants' presently claimed invention. These references provide even less relevant teaching than the secondary references and do nothing to compensate for the many deficiencies in the teachings of both the primary and secondary references. Accordingly, there is no teaching or suggestion provided by the art or the references themselves to combine the primary, secondary and tertiary references. Further, were one to combine these references, there is still no teaching or suggestion that would lead one of skill in the art to make the modifications necessary to arrive at Applicants' claimed invention with a reasonable expectation of success.

In view of the complete and disparate teachings of the three primary references of Ye et al., the '645 patent and the '504 patent, which stand in contrast to and teach away from Applicants' presently claimed invention, there is no suggestion or motivation, either provided by the references considered in their entireties, or in the art, for one skilled in the art to combine the teachings of these references, or to make the modifications necessary to arrive at Applicants' invention as presently claimed. The surprising properties exhibited by Applicants' presently claimed invention are not contemplated or suggested by the cited art, taken alone or in combination.

Based on the disparate nature of the primary references and their clear teaching away from Applicants' presently claimed invention, as well as the lack of compensatory teaching in the secondary and tertiary references, there is no teaching or suggestion, either in the references themselves or in the art, that would lead the skilled person in the art to combine the teachings of these references so as to arrive at or achieve Applicants' claimed invention with a reasonable expectation of success. Because none of the cited references, alone or combined, teach or suggest all of the limitations of Applicants' presently claimed invention, it is

submitted that a *prima facie* case of obviousness has not been established. Withdrawal of this §103(a) rejection is thus respectfully requested.

Claims 21, 22, 46-56 and 59-61 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 99/56785, in view of Kropp et al. (1996, *J. Urol.*, 155:2098-2104), Vandenburgh (U.S. Patent No. 6,503,504, hereinafter "the '504 patent") and McDowell et al. (U.S. Patent No. 6,171,340, hereinafter "the '340 patent"). The Examiner opines that it would have been obvious to one of ordinary skill in the art to combine muscle stem cells or SIS "to form a new composition for tissue repair with a reasonable expectation of success, wherein the two components could be attached together or just [applied] at the same time."

Applicants respectfully disagree that the presently claimed invention would be obvious in view of the above-cited combination. As discussed in detail above, WO 99/56785 teaches muscle derived cells that can be genetically engineered to deliver biomolecules to tissues, as well as their method of preparation and use in muscle tissue repair. WO 99/56785 is silent regarding Applicants' inventive compositions and preparations which provide point of service compositions and preparations that were newly found by Applicants to have unexpected properties and advantages upon rapid admixture and use in tissue and organ treatment or repair. More specifically, Applicants have unexpectedly discovered that functional muscle-derived stem cell and matrix material compositions and preparations form stable biomatrices having altered biomechanical properties so as to provide 2- and 3-dimensional structures that exhibit contractility and can be innervated, thus enhancing their function. In contrast, WO 99/56785 does not teach or suggest a muscle-derived stem cell biomatrix that (i) can be used following admixture of the muscle-derived stem cell and matrix material components without prolonged incubation or culturing, unlike the cell matrix compositions described in the art at the time, or that (ii) has the properties of Applicants' presently claimed invention.

Kropp et al. teach the use of a SIS graft for bladder augmentation in dogs. Kropp et al. use dogs to extend the studies previously done using rats. Kropp et al. merely disclose that a SIS graft supports the regeneration of bladder smooth muscle, based on their studies in dogs.

As discussed at length above, the teachings of Vandenburgh are antithetical to Applicants' presently claimed invention, because Vandenburgh's disclosed organoids require long preparation times and an extraneous apparatus or vessel. McDowell et al. teaches articulating joint and cartilage repair involving attachment of a cell or cell matrix to prosthetic shields and/or spacers. Neither Vandenburgh nor McDowell, when combined with the teachings of WO 99/56785, motivates or provides impetus for one skilled in the art to make the modifications necessary to arrive at Applicants' invention. The teachings of the cited references are disparate and even antithetical to the presently claimed invention. Neither the art nor the references suggests a combination that would lead to Applicants' presently claimed invention with a reasonable expectation of success.

At the time of Applicants' invention, the art taught that combining cells with a matrix required and involved long culturing, incubation, and/or preparation times to achieve a matrix product for use in a given treatment. Applicants provide to the art novel compositions and preparations having the ability to form useable muscle-derived stem cell biomatrices shortly (e.g., 12 hours or less) after admixture, without a need for long-term incubation or culturing of the muscle-derived cells with the matrix material. This is an unexpected and surprising finding, which is not remotely contemplated or suggested in the art or in the cited references. The cited references, alone or in combination, do not lead one to modify the teachings of the references so as to achieve Applicants' invention. Moreover, there is no suggestion or teaching provided by this art to make a combination that would lead to Applicants' invention with a reasonable expectation of success. It is submitted that the cited art, and not Applicants' disclosure, must teach or suggest a combination and a reasonable expectation of success. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Because none of the cited references, alone or combined, teach or suggest all of the limitations of Applicants' presently claimed invention, it is submitted that a *prima facie* case of obviousness has not been established. The combination of the teachings of the above-cited references considered in their entireties does not negate the patentability of Applicants' claimed invention. Accordingly, withdrawal of this rejection is respectfully requested.

Double Patenting

Claims 21, 22, 38, 40-44, 46-56 and 61 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 115 of patent application U.S. Serial No. 09/549,937. According to the Examiner, the conflicting claims are not identical, but are not considered to be patentably distinct from each other.

Applicants respectfully request that this rejection be held in abeyance until the claims in the instant application have been deemed to be allowable, at which time, Applicants will file an appropriate terminal disclaimer.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this amendment and response, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311**, Reference no. **28682-502,** Customer Number: **35437**.

If the Examiner believes that it would be helpful to discuss the application to advance the prosecution of the application and claims to allowance, he is respectfully requested to telephone applicants' undersigned representative at (212) 692-6742 and is assured of full cooperation in this effort.

Respectfully submitted,

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.

Date: November 3, 2004

By: Leslie A. Serunian
Leslie A. Serunian
Registration No. 35,353

Correspondence Address:
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
Chrysler Center
666 Third Avenue
New York, New York 10017
Telephone: (212) 935-3000
Facsimile: (212) 983-3115
Direct Tel.: (212) 692-6742

Express Mail Label No.: EL991158297 US